STATEMENT OF WORK

A. **BACKGROUND**

The Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), is charged with providing pharmaceutical support for clinical trials sponsored by the National Cancer Institute. The DCTD sponsors intramural and extramural research on the clinical development and evaluation of potentially effective cancer treatments.

One of the responsibilities of the PMB in supporting this clinical research is to manage a contractor that provides an adequate facility and project team to store and distribute clinical agents and maintain adequate records of all aspects of the process. The Clinical Drug Repository is currently open and accessible during regular business hours (8:30 AM - 5:00 PM, Eastern Time), Monday through Friday, except for official Government holidays. An occasional evening, night, or weekend emergency shipment has been necessary.

The Contractor is responsible for receiving shipments of investigational and non-investigational agents from a variety of pharmaceutical manufacturers throughout the U.S. and the world. These shipments vary in size, but the number of units received may run in the tens of thousands. Dosage forms currently used include: injectable products in vials, syringes, and ampules (many of which require refrigerated or frozen storage); vaccine, peptide, and monoclonal antibody preparations, which may require -70^{o}C frozen storage; solid and liquid oral dosage forms; and a topical preparation. When a shipment arrives at the Contractor managed Clinical Agent Repository, it shall be carefully checked for conditions on arrival (e.g. broken vials, refrigerated items not adequately cold) and stored under labeled storage conditions (e.g. controlled room temperature, refrigerated, frozen, -70^{o}C frozen storage). Appropriate entries shall be made in the PMB computer application for inventory management and tracking (Drug Authorization and Review Tracking System - DARTS). Each lot of agent shall be approved as suitable for clinical use by the Project Officer, PMB, or designated PMB pharmacist before the lot is released to the active inventory for shipment to clinical investigators. At any time, a total of approximately 600,000 units may be stored at the clinical repository.

When a registered NCI investigator at a clinical site requires an agent supply for an NCI study, the site submits an order called a Clinical Drug Request (CDR). This request, which specifies the protocol, agent, strength and number of units needed, as well as other necessary information, is sent for approval to PMB staff. Upon request approval, Shipping Records are then printed at the Clinical Agent Repository, where the specified numbers of each type of dosage form are repacked into a shipping container in such a way that the agents will reach the clinical site intact, at the proper temperature, and in good condition. Types of shipments include: dry ice; Dangerous Goods (DG); infectious agents; wet ice; international; and combinations of the previous types. Rush deliveries are often necessary. Computerized record keeping accompanies every step of the receipt, storage, distribution, and final disposition of these agents.

This contract effort also provides pharmaceutical support for randomized, double-blind clinical trials of a number of agents with potential usefulness in treatment and/or prevention of cancer. The Contractor shall provide storage, patient-specific blinded labeling, distribution to individual clinical sites, and computerized record keeping. Approved orders for patient-specific shipments are received from PMB, and patient number and initials, treatment assignment, date dispensed, and lot number are downloaded from DARTS. Individual, blinded container labels shall be printed and checked, and the appropriate product (drug or placebo) pulled, labeled, and checked by a pharmacist before shipping to the investigator. The contract is currently supporting 19 randomized, double-blind clinical trials.

The mission of CTEP has expanded to include pharmaceutical support of high-priority NCI -supported clinical trials where CTEP does not hold the IND and where accrual would be significantly less or significantly slower without PMB distribution of agent. It is essential that these trials use the CTEP Enterprise System, including investigator registration, PMB order approval (part of DARTS), the Clinical Data Update System (CDUS), and Adverse Event Expedited Reporting System (AdEERS). CTEP would like

this contract to incorporate this expanded activity that will involve protocol specific agent forecasting, the establishment of a pricing structure of the cost for storage and distribution of study agent, and the invoicing for these trials. The recovery of costs is handled through the Clinical Supplies Agreement (CSA) mechanism.

Definitions

1. Active Inventory Agents

   Those agents that have been cleared by a PMB pharmacist to be used in human subjects on clinical trials.

2. Agent

   Drug product (e.g., chemical drug), biologic product (e.g., cytokine, monoclonal antibody, gene therapy, vaccine), or other therapeutic anticancer agent used to treat or prevent cancer in support of NCI-sponsored clinical trials.

3. CSA Trials

   Clinical research studies that involve a Clinical Supplies Agreement (CSA) that addresses the cost of storage and shipping for one or more of the agents used on the trial.

4. DARTS Drug Authorization and Review Tracking System.

   This is a module of the CTEP Enterprise computer application that PMB uses for all agent inventory management and tracking.

5. IATA

   The International Air Transport Association. It is the prime vehicle for inter-airline cooperation in promoting safe, reliable, secure and economical air services - for the benefit of the world's consumers. The modern IATA is the successor to the International Air Traffic Association founded in the Hague in 1919 - the year of the world's first international scheduled services.

6. Pharmacist check

   Blinded study agents that leave the repository are required to be examined for accuracy by a registered pharmacist.

7. PMB Pharmaceutical Management Branch, National Cancer Institute

8. Quarantine Inventory Agents

   Those agents that are not fit for human use.

9. Shipping Configuration

   The way a package is put together for shipping--including the container and materials used, the amount of material used, and the positioning of the agent within the package.

10. Strength

    The amount of active ingredient.

11. Unit:

The smallest physical package of an individual agent that can be shipped.

Physical packages include, but are not limited to: vials (1 mL - 500 mL in individual boxes or not); ampules (1 mL - 10 mL in individual boxes or not); bottles or unit dose boxes of tablets and capsules; tubes of ointment (in individual boxes or not); bottles of powder for oral solution; syringes; and boxes containing two different types of vials or a combination of a vial and an ampule.

C.1. STATEMENT OF WORK

Independently and not as an agent of the Government, the Contractor shall operate a Clinical Agent Repository and shall furnish all the necessary services, qualified personnel, materials, equipment, and facilities not otherwise provided by the Government as needed to perform the Statement of Work below:

a. Receipt of Clinical Agents

1. The Contractor shall receive shipments of agents from a variety of domestic and international sources, including, but not limited to, manufacturers, packagers, pharmaceutical companies, and pharmaceutical suppliers. The number of shipments to be received shall involve 400,000 to 700,000 units per year.

2. For agents being shipped from a foreign source, coordinate with the Customs Broker at the point of US entry and arrange for delivery from the Broker to the repository. (Note: Dulles International Airport is currently designated by NIH to handle incoming foreign shipments). Approximately 20 shipments of study agents are received from international suppliers per year.

3. Inspect contents and condition of shipment upon receipt. Reconcile discrepancies with shipping lists, note conditions of materials received, inspect labeling. Provide to the Project Officer by facsimile and through DARTS within 3 hours of arrival of the agent the following information:

   i. strength
   ii. lot number
   iii. amount received
   iv. any problems or discrepancies and
   v. a copy of the agent label

b. Storage of Clinical Agents

6. The Contractor shall store an average of 600,000 units of agents in a secure, controlled-temperature warehouse with an adequate fire-protection system, at each agent's required storage conditions. These storage conditions may include -70 degrees Centigrade, -20 to -10 degrees Centigrade, 2 to 8 degrees Centigrade, or controlled room temperature. Provide sufficient monitoring of such storage conditions to guarantee and document continuous proper storage.

7. Quarantine and active inventory agent items shall be stored separately.

8. The Contractor shall insure that required storage conditions are maintained at all times. All storage facilities must have appropriate monitoring and back up systems to maintain the required storage conditions. Monitoring systems must be continuos and provide immediate notification to the Contractor in the event storage conditions for any agent are not met. The Contractor's monitoring system must include quality control that validates the accuracy of the monitoring systems. Electrical power generation systems used for backup electrical power for maintaining storage conditions must be installed in accordance with all Federal, State and Local regulations concerning the installation of back up electrical power generators. The electrical power generation systems must be able to restore power such that all storage conditions are maintained.

9. The Contractor shall insure the physical security of all agents and Government owned/furnished property. This includes, but is not limited to, prevention of unauthorized entry, theft, misuse, or damage to agents or Government-owned property. At a minimum, the Contractor must also insure that the facility has fire suppression capable of minimizing damage in the event of fire. Fire suppression for agents stored at room temperature and stored files may not be water based sprinklers. The Contractor shall include a quality control that insures the reliability of all fire suppression systems.

10. The Contractor shall meet all applicable U.S. Food and Drug Administration Current Good Manufacturing Practice guidelines on storing and distributing agents, as specified in Title 21, Code of Federal Regulations, Parts 210 and 211 including mapping validations for all refrigeration units.

c. Inventory Control/Data Management

1. Perform a complete physical inventory, at a single point in time, of all agents semi- annually. Perform limited, special inventory checks as requested by the Project Officer. A physical inventory of each agent shall be conducted monthly. Any discrepancies between the physical inventory and the computer inventory shall be reported to the Project Officer within 3 calendar days.

2. Input to DARTS all repository related data including but not limited to:

   Daily shipping dates
   Agent receipt information
   Return agent information
   Agent destruction information

d. Shipping/Distribution

1. The Contractor shall, as needed or requested, pickup and deliver paperwork, agents, and other contract related materials to and from the PMB, the NIH Clinical Center, and the Bethesda Naval Hospital. Pickup of international shipments from the customs broker at the point of US entry may be required.

2. As directed by the Project Officer, ship agents, in the quantity specified and in accordance with all labeling and packaging required, to consignees. Shipping configurations shall be validated.

3. Prepare all documentation required for the shipping of agents.

4. Process, on a daily basis, authorized requests for clinical agents. Contractor shall ship between 400,000 and 700,000 units per year. Emergency (same day) shipments shall be required occasionally as will shipments after normal hours and on weekends. There shall be contract staff available 24/7 for emergency requests.

5. Ensure that all handling of agents between storage and distribution is performed in a manner that assures continued viability of the agent.

6. Store all Shipping Records, Return Drug Lists, blinded study documents, inventory records, Quality Control Validation documentation, and other documentation associated with the performance of the contract. Store Material Safety Data Sheets and lot-specific pharmaceutical information sheets, and include in shipments, as directed by the Project Officer. Include a PMB Newsletter, supplied by the Government, in shipments as directed by the Project Officer.

7. Staff preparing shipments of agents classified dangerous must be certified in Dangerous Good (DG) shipping.

8. Contractor is responsible for the viability of each unit of agent from receipt to final destination point, including but not limited to, receipt, storage, preparation of agent for shipping, and shipping.

e. Labeling/Dispensing of Blinded Study Agents

1. Receive, store, and inventory shipments of bottles, vials, tubes, or blister cards of study agents for blinded studies. Containers must be carefully checked to ensure that the agent/placebo and its labeling is indeed blinded. Products may arrive with unblinded labeling, so procedures must be in place to ensure that such labeling is removed and attached to the dispensing log at the time the final patient label is attached. The lot number shall be retrievable from DARTS after the individual patient labeled bottle is dispensed.

2. Dispense PMB approved (via DARTS) orders for approximately 115,000 units of patient-specific agents per year. This includes printing and checking individual, blinded container labels and dispensing logs, pulling the appropriate study agent (drug or placebo), labeling each container, performing quality control validations, and shipping of the agent as specified. Quality control validation shall be done for each unit and will include review of the source document (order), final container, and intermediate paperwork. Labels shall be affixed on-site. The quality control validation must be performed by a pharmacist.

3. There shall be dedicated space for performing blinded studies activities and only blinded studies activities shall be performed in that space.

f. Labeling of Open-Label Agents

1. Relabel approximately 24,000 units of agents per year, such as bottles of tablets or capsules, ampules, or vials, as necessary to meet U.S. FDA requirements for investigational agents and NCI guidelines for completeness and clarity. Label content shall be specified by the Project Officer. Labels shall be affixed on-site. Appropriate record keeping and quality assurance measures shall be required.

2. Generate approximately 120,000 auxiliary labels per year and affix them to individual units of medication or outside packages as specified by the Project Officer. Labels shall be affixed on-site.

g. Processing and Disposal of Returned Agents

1. Receive recalled, expired, or unused agents returned from clinical investigators. All agents returns should be accompanied by a Returned Drug List form completed by the investigator returning the agent. Process returned agents in conformance with local, state, and federal regulations. Agents shall be processed in a matter that provides protection (including a Biologic Safety Cabinet) for personnel handling the returned chemotherapeutic and biologic agents and the environment.

2. Compare the Returned Drug List with the agents received and note any discrepancies on the form. Prepare and send return receipts to clinical investigators as requested by the site. Document all returns in DARTS.

3. Store returned agents at room temperature, separate from clinical supplies, until final disposition. Dispose of returned agents as directed by the Project Officer, and in accordance with local, state, and federal regulations. This includes destruction of the agent or return to the manufacturer of the agent.

h. Clinical Supplies Agreements (CSAs)

In the context of CTEP's expanded mission to provide pharmaceutical support for high-priority trials, the contractor will establish an integrated unit that will handle all aspects of the agents involved in CSAs except for the actual development of the CSA (to be handled by CTEP's Regulatory Affairs Branch) and the ordering of the agents (to be handled by PMB). Activities include, but are not limited to:

h. In conjunction with the Project Officer, establish a pricing structure

i. Provide the Project Officer with cost estimates for each new CSA

j. Create protocol specific agent forecast reports

d. Track all CSAs, invoices, payments, clinical supplies, expenses

i. Site Visits/Outside Visitors

1. The Contractor's facility may be site visited by Government staff approximately 8 times per year. All site visits shall be coordinated by the Contractor's authorized representative or Principal Investigator with the Contracting Officer, Contract Specialist, or Project Officer.

2. With the exception of visitors required by law or regulation, no outside visitors are authorized to perform site visits of the facility. Certain outside parties (such as collaborators) may site visit the facilities and view selected Standard Operating Procedures at the approval of the Project Officer and in coordination with the Principal Investigator. The Contractor shall obtain signed confidentiality agreements from all outside parties prior to entrance into the facility or viewing of Standard Operating Procedures. Unless required by law, no inspections by drug companies are allowed.

j. Security/Safety

1. All personnel performing work under this contract shall be bonded employees.

2. All personnel shall be trained in the handling and disposal of hazardous material.

3. All pharmacists performing work under the contract shall have a current license, in the state (or District of Columbia) in which the repository is located, at all times.

k. IT Support

1. The Contractor will provide assistance to the Government for DARTS development, enhancement, and maintenance.

2. The Contractor will be required to interface with the NIH network to access DARTS. The Contractor will be required to have computers that can interact with Government computers and must follow all data safety protocols for access to the NIH network.

l. Certifications/Permits/Licenses

The Contractor shall obtain and maintain current, all applicable certifications, permits, and licenses required for the performance of the contract. These include, but are not limited to:

1. State Board of Pharmacy Permits

2. Hazardous Use Certificates

3. EPA Regulated Waste Licenses

4. State Special Waste Permits

5. IATA Dangerous Goods Training Certifications

6. Individual pharmacist licenses

m. Transition

1. Phase-In

The Contractor shall move all agent inventory, files, and Government provided equipment from the predecessor Contractor's facility to its facility within 30 calendar days of contract award. The Contractor shall transfer agent inventory under proper and documented controlled temperatures. This transfer of inventory, files and equipment shall be performed in coordination with the predecessor Contractor, the Contracting Officer, and the Project Officer. The Contractor shall meet, and work with, the predecessor Contractor to insure that work operations are fully understood.

2. Phase-Out

In accordance with the delivery schedule, the Contractor shall prepare and submit a Phase Out Plan to the Project Officer and the Contracting Officer. The plan shall include, but not be limited to, details on the transfer of filed material and documents and the transfer of inventory and equipment. Upon review and approval by the Contracting Officer and Project Officer of the Contractor's Phase Out Plan, the Contractor shall meet with and provide the successor Contractor with detailed briefings regarding the policies and procedure for managing all aspects of the project. The Contractor shall make the facility available to the successor Contractor to effect the transfer of all contract related items to be transferred to the successor Contractor. This includes any inspections to determine the personnel and equipment required for the transfer as well as the physical transfer.

Government Property

Government Property currently utilized under this contract and available for use is included in this document as Exhibit 4.